

Perfusion Functional Magnetic Resonance Imaging

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Introduction

Imaging sequences based upon blood oxygenation level dependent (BOLD) contrast are currently the predominant method for functional magnetic resonance imaging (fMRI) of the brain. BOLD weighted sequences offer both high contrast-to-noise ratio and good temporal resolution. The BOLD signal reflects the total amount of deoxyhemoglobin (dHbO_2), and is thus a complex function of cerebral blood flow (CBF), the cerebral rate of oxygen metabolism (CMRO_2), cerebral blood volume (CBV), and magnetic field strength. As a result, the interpretation of changes in the BOLD signal can be complicated by variations in these physiological quantities due to factors such as age, disease, or the presence of vasoactive agents [1]. Perfusion fMRI based upon arterial spin labeling (ASL) methods offers a useful complement to BOLD fMRI. It can provide quantitative measures of both baseline and functional changes in CBF that can aid in the interpretation of the BOLD signal change. Changes in CBF are thought to be more directly linked to neuronal activity than BOLD, so that perfusion fMRI also has the potential to offer more accurate measures of the spatial location and magnitude of neural function. Perfusion fMRI also has some practical advantages, including an inherent insensitivity to low-frequency fluctuations commonly observed in fMRI experiments and the ability to take advantage of imaging sequences (e.g. spin-echo) that are insensitive to susceptibility induced off-resonance effects.

Cerebral Blood Flow

Cerebral blood flow or perfusion is a measure of the rate of delivery of arterial blood to a capillary bed in tissue [2]. The standard unit of measurement for CBF is (milliliters of blood)/(100 grams of tissue)/ (minute), and a typical value in the human brain is 60 ml/(100 g)/minute. Assuming an average brain tissue density of 1 g/ml, the average CBF may also be written as 60 ml/(100 ml)/minute = 0.01 s^{-1} . In a typical ASL experiment, about 1 second is allowed for the delivery of blood. This corresponds to 1 ml of blood delivered to 100 ml of tissue. As a result, the overall magnetic resonance (MR) signal due to the delivered blood is only about 1% of the total signal due to the tissue. This small percentage contributes to the low intrinsic signal-to-noise ratio (SNR) of ASL methods.

Overview of Arterial Spin Labeling

Most arterial spin labeling methods measure CBF by taking the difference of two sets of images: **tag images**, in which the magnetization of arterial blood is inverted or saturated, and **control images** in which the magnetization of arterial blood is fully relaxed. The basic steps are as follows:

- 1) Arterial blood flowing toward the region of interest (ROI) is tagged by magnetic inversion or saturation (see Figure 1). This tagged blood flows into the imaging slices or volume and also relaxes toward equilibrium with the longitudinal relaxation time constant of blood (see red curves in the bottom half of Figure 1).
- 2) After a delay TI (known as the inversion time) to allow for inflow of tagged blood, an image is acquired in the slice(s) or volume of interest. This image is referred to as the **tag image**.
- 3) As discussed above, the delivered blood signal is only about 1% of the static tissue signal. In order to remove the contribution of the static tissue to the tag image, a **control image** of the same

slice is acquired in which inflowing blood is not tagged. The magnetization of this control image is shown by the dashed blue lines in the bottom half of Figure 1.

4) Taking the difference of the control and tag images yields an image $\Delta M = M_{control} - M_{tag}$ that is proportional to CBF. This is shown as the difference of the blue and red lines in Figure 1.

5) Tag and control images are typically acquired in an interleaved fashion, and the running difference of the control and tag images is used to form a perfusion time series (see Figure 3 and Section on Processing of ASL data).

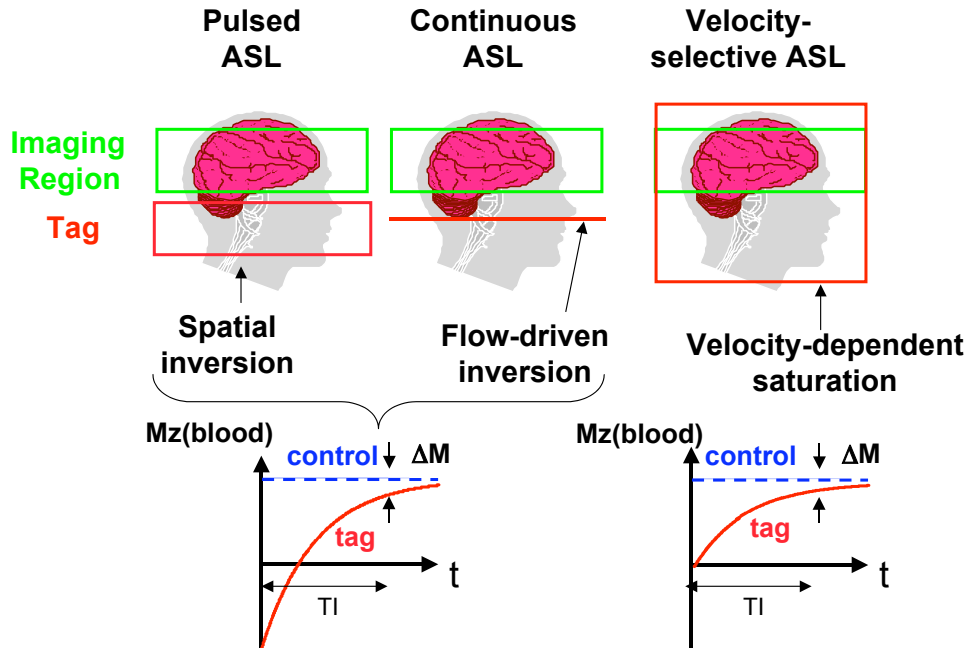


Figure 1. Pulsed, continuous, and velocity-selective ASL methods use various methods to either invert or saturate the magnetization of arterial blood. The difference ΔM between control and tag images is proportional to CBF.

Arterial Spin Labeling Methods

There are currently three classes of ASL methods as summarized in Figure 1.

Pulsed ASL (PASL) – tagging based on location. In these techniques, short (5-20ms) RF pulses are used to saturate or invert a slab of magnetization that is proximal to the region of interest. These techniques have the advantages that they provide high inversion efficiency and use little RF power. Disadvantages are that they depend on the coverage and uniformity of the transmit RF field to determine the geometry of the applied tag. Pulsed ASL techniques include EPISTAR [4], FAIR [5], PICORE [6], and many other variants.

Continuous ASL (CASL) – tagging based on location and velocity. In continuous ASL, long (1-3s) RF pulses are used in conjunction with a static gradient field to irradiate a narrow plane of spins with RF energy. The plane is chosen proximal to the region of interest so that inflowing arterial blood flows through in a direction that is roughly normal to the plane. When the amplitude of the RF and gradient fields are properly adjusted, flowing blood undergoes adiabatic flow dependent inversion when traversing the irradiated plane [7]. Because the tag can be applied closer to the region of interest (on average), this can result in a higher overall tagging efficiency than pulsed techniques. However, this technique requires a large amount of average RF power and can

be limited by specific absorption rate (SAR) considerations at higher fields. Some of these limitations are addressed in a recently introduced form of CASL, dubbed pseudo-CASL, that uses repeated RF pulses instead of a continuous RF wave [8]. A detailed comparison of pulsed and continuous ASL techniques can be found in [9].

Velocity selective ASL (VS-ASL) – tagging based on velocity. In this technique [10], an RF pulse train is applied that selectively saturates flowing spins with no spatial selectivity. Because it tags all blood that is flowing above a selected cutoff velocity this technique has the advantage that the applied tag is close to all the target tissue. This results in a small and uniform transit delay for the delivery of the tagged blood to the tissues of interest (see below regarding transit delays).

Perfusion Quantitation

The ASL difference signal ΔM is proportional to CBF but also has a complex dependence on a number of physiological parameters. Variations in these physiological parameters can cause systematic errors in the CBF measurements. **The goal of quantitative ASL methods is to minimize these errors.** The primary sources of errors are: 1) the **transit delay** Δt between the tagging region and the imaging slice, 2) the **temporal width** τ of the arterial bolus in PASL techniques, 3) the presence of intravascular blood that has not yet perfused its target capillary bed, 4) the dependence of relaxation on the exchange of water between blood and tissue compartments, and 5) the clearance of water by outflow. Of these, the errors due to exchange and clearance are typically negligible, and so we will focus on the first three sources [3].

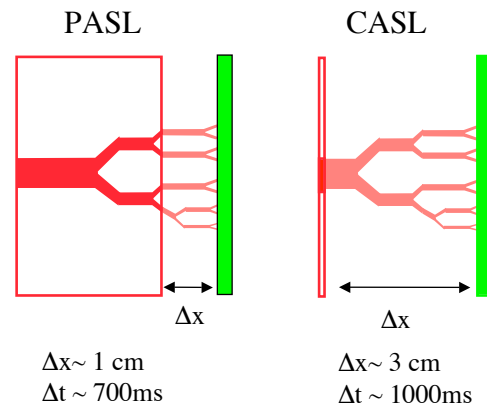


Fig 2. Illustration of spatial gaps between the tagging (red) and imaging (green) regions in PASL and CASL and the associated transit delays.

As shown in Figure 2, transit delays arise in spatial tagging methods because of the need to place the tagging slab in PASL or the tagging plane in CASL some distance (1 to 3 cm) from the imaging slice in order to minimize the perturbation of spins in the imaging region. To allow all of the tagged blood to travel from the tagging region to the imaging region, the inversion time TI must satisfy the condition $TI > \Delta t + \tau$ where Δt is the transit delay and τ is the temporal width of the tagged bolus [6]. Although increasing the inversion time reduces the sensitivity to transit delays, it also reduces the magnitude of the difference signal ΔM which is decaying exponentially with a relaxation time that is of the same order as the transit delay (the T_1 of blood is approximately 1300 ms at 1.5T). Thus, the inversion time should be chosen to be large enough to reduce transit delay effects. Typical inversion times are 1000 ms and 1400 ms for CASL and PASL, respectively. In contrast to CASL and PASL, transit delays are typically negligible in VS-ASL because the velocity-selective tagging process saturates arterial blood that with velocities down to 1 to 2 cm/s, corresponding to vessels (roughly 50 to 100 micron arterioles) that are close to the capillary bed and within the imaging region. This insensitivity to transit delay makes VS-ASL a particularly attractive method for functional ASL studies of subjects, such as stroke patients, who may exhibit long transit delays.

In CASL methods the temporal bolus width τ is determined by temporal duration (typically 1 to 3 seconds) of the continuous inversion pulse. However, in PASL methods the temporal width depends on the velocity of arterial blood in the tagging region, which typically increases with functional activation. To reduce the sensitivity to the temporal width, a spatial saturation pulse is applied to the tagging region at a time TI_t after the inversion pulse. This is referred to as the QUIPSS II modification [6]. If $TI_t < \tau$, then the temporal width of the bolus is TI_t , and the

measured signal is proportional to the product of CBF and TI_l . Variations of the QUIPSS II modification are also applicable to velocity-selective ASL.

A related source of error is the presence of tagged blood in the arteries and arterioles that has entered the imaging slice but is destined to perfuse more distal slices. If the image is acquired before this blood has time to leave the imaging slice, the intravascular signal will contribute to the ASL difference signal and lead to an overestimate of CBF. Typically, this is not a problem when using pulse sequence parameters that also control for transit delays. In addition, flow-weighting gradients can be used to crush the intravascular signal at the cost of a reduction in the SNR of the desired difference signal [11].

Processing of ASL data

In most ASL fMRI experiments, control and tag images are acquired in an interleaved fashion, as shown in Figure 3. A perfusion time series is then formed from the running subtraction of the control and tag images. An example of this process is shown in Figure 3, where the perfusion images are formed from the difference between each control image and the average of the two surrounding tag images or from the difference between the average of two surrounding control images and a tag image. The type of

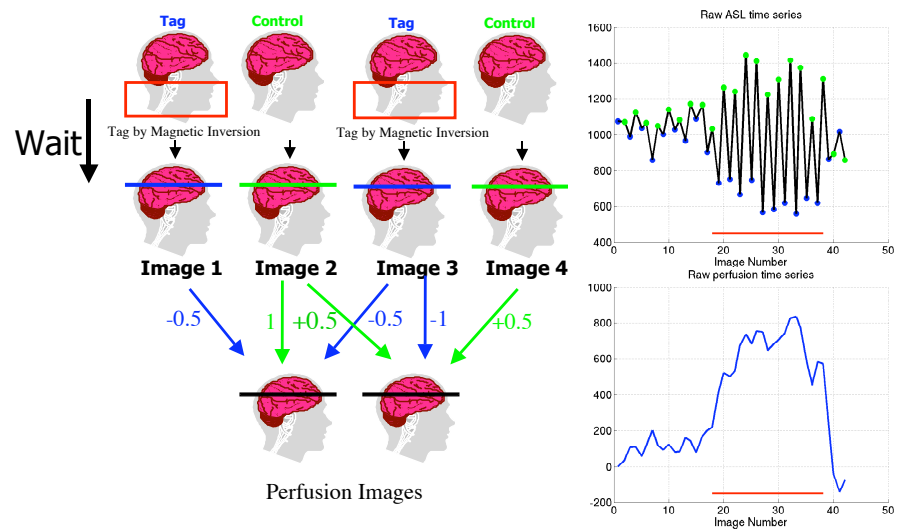


Fig 3. Formation of a perfusion time series from the “surround subtraction” of control and tag images. An example time series of control (blue) and tag (green) signals is shown in the upper righthand plot. The perfusion time series created by surround subtraction is shown in the lower righthand plot. The red bars indicates the time of stimulus.

tag image. The type of differencing shown in Figure 3 is referred to as *surround subtraction*, and represents one specific approach to the ***filtered subtraction*** of control and tag images. Other common approaches are *pairwise subtraction* and *sinc subtraction*. These approaches all share the property that they can be modeled as the modulation of the control and tag images (e.g. multiply all control images by +1 and all tag images by -1) followed by convolution with a filter [12]. For fMRI experiments with block designs (e.g. long periods of on/off), surround and sinc subtraction tend to provide the best performance. In contrast, for randomized event-related experimental designs, pair-wise subtraction can provide better performance (e.g. less filtering of the hemodynamic response function) [12]. However, all filtered subtraction approaches lead to inevitable broadening of the hemodynamic response function. Unfiltered approaches based upon general linear models of the ASL experiment can be used to eliminate this broadening and can also lead to improvements in statistical power [13, 14].

As with BOLD fMRI experiments, cardiac and respiratory fluctuations are a major source of noise in ASL experiments, especially at higher field strengths. Since the inherent SNR of ASL methods is typically much lower than that of BOLD fMRI, the need for methods to reduce physiological noise is especially pronounced. Retrospective image based methods have been shown to significantly reduce physiological noise in ASL data [15]. An example is shown in Figure 4.

Simultaneous Estimates of CBF and BOLD

ASL data for fMRI are often acquired with single-shot acquisition methods such as echo-planar imaging (EPI) or spiral readouts. In addition to their sensitivity to flow introduced by the tagging process, these images can also exhibit BOLD contrast. For example, with gradient echo readouts, the images exhibit a BOLD weighting. Dual echo acquisitions are particularly useful for simultaneous perfusion and BOLD imaging. Images acquired at a short echo time (e.g. 3 ms) can be used to form a perfusion time series with relatively little BOLD weighting, while images acquired at a later echo time (e.g. 30 ms) can be used to form the BOLD time series.

A BOLD time series can be formed from the control and tag images through a running average approach that is analogous to the filtered subtraction approach used to form the perfusion time series. In general, the BOLD time series is formed by the convolution of the control and tag images with a lowpass filter [12]. For example, the method analogous to surround subtraction would be a surround average consisting of the average of each image with the average of its two nearest neighbors. The BOLD time series are inherently flow-weighted because of the tagging process. In pulsed ASL experiments the flow-weighting can be reduced by the application of a presaturation pulse applied in the imaging plane either immediately prior to or immediately after the application of the tagging pulse [12, 16]. Figure 5 shows examples of the CBF and BOLD time series measured using a PICORE QUIPSS II pulse sequence [6] with a pre-saturation pulse [17].

Temporal Resolution

The temporal resolution of perfusion fMRI is inherently poorer than BOLD fMRI because of the necessity to form tag and control images and to allow time for blood to be delivered from the tagging region to the imaging slice. In a typical pulsed ASL experiment, a repetition time (TR) of 2 seconds or more is used, so that one tag and control image pair is acquired every 4 seconds. By comparison, the temporal resolution of BOLD fMRI is typically 1 to 2 seconds and can be as low as 100 ms for specialized applications. Methods for improving temporal resolution include turbo-ASL [18] and single-shot ASL [19]. In turbo-ASL, a control image is acquired after the inversion pulse at a delay (typically 100 ms) that is too small for blood to have flowed into the imaging slice. A tag image is then acquired at an interval of TR (typically 1 second) after the control image. In

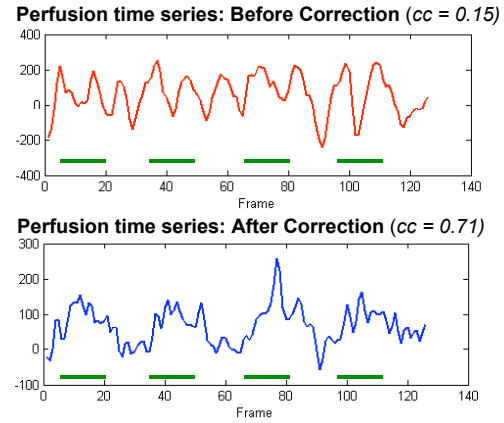


Fig 4. Example of a perfusion time series before (red curve) and after (blue curve) the application of physiological noise correction. The green bars indicate the times when a stimulus was applied.

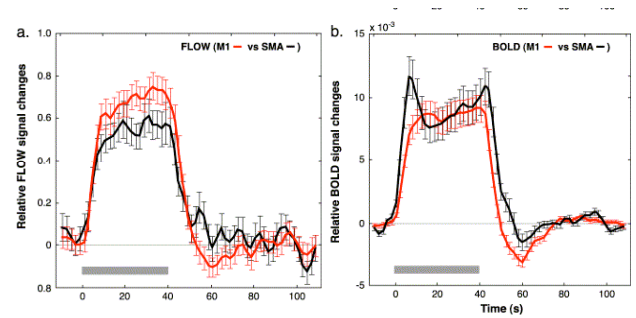


Fig 5. CBF (left) and BOLD (right) time series as measured in the primary (M1, red) and supplementary motor areas (SMA, black) using a PICORE-QUIPSS II sequence with dual-echo spiral readout [17].

single-shot ASL, background suppression is used to suppress static tissue, thus eliminating the need for a control image. While these methods can improve temporal resolution, the quantitation of the resultant ASL signals is more complicated than more standard methods [20].

SNR and CNR

As discussed on the first page, the SNR of ASL methods is inherently low because the inflowing blood magnetization is typically only about 1 percent of the tissue. The low SNR combined with the poor temporal resolution of ASL results in a low contrast-to-noise ratio (CNR) for quantitative ASL fMRI experiments as compared to BOLD. Due to the low inherent SNR of ASL methods, noise reduction methods such as the physiological noise reduction method discussed above should be used wherever possible. Background suppression methods that attenuate the static tissue component also have the potential to reduce noise, but their application for simultaneous CBF/BOLD experiments is not straightforward [21]. For functional mapping experiments where quantitation of CBF is not required, non-quantitative versions of ASL, such as turbo-ASL [18] and close-tag CASL [22], can be used to improve the CNR. For example, the CNR of close-tag continuous CASL at 1.5T has been shown to approach that of the BOLD signal for a finger-tapping experiment.

Spatial Coverage

At present, most ASL fMRI studies use 2D multi-slice acquisition methods in which the data are acquired on a slice-by-slice basis. For CASL and PASL methods, the slices are typically acquired in an inferior-to-superior manner so that slices that are further from the tagging region are acquired at later times. The number of slices that can be acquired depends on the (a) acquisition time for each slice, (b) the time TR-TI that is available for slice acquisition, and (c) the need to acquire slices before the difference signal ΔM has decayed away due to the longitudinal relaxation of blood. Due to these considerations, ASL studies typically acquire a smaller number of slices (e.g. 3 to 15) than a whole-brain BOLD studies (e.g. 30 to 40 slices), with thicker slices (e.g. 5 to 8 mm) than would be used in a BOLD study (e.g. 3 or 4 mm). Recently, ASL fMRI studies with single-shot 3D acquisitions have been demonstrated [23, 24]. 3D acquisition methods can lead to reduced susceptibility artifacts, are well-suited to the use of background suppression methods, and are a natural match for the non-spatial tagging scheme used in VS-ASL. However, 3D methods are not well suited for simultaneous measurements of CBF and BOLD.

Applications of ASL in functional MRI

Quantitative Assessment of Brain Activity

Because it can provide a quantitative measure of a fundamental physiological quantity (CBF), ASL has the potential to better reflect neural activity as compared to BOLD, which is a complex function of a number of physiological variables. For example, the findings of one ASL study suggest that the relation between CBF changes and neural activity may be more linear than the relation between BOLD and neural activity [25]. Several studies have shown that ASL measures can exhibit decreased inter-subject and inter-session variability as compared to BOLD, possibly reflecting a more direct link between CBF and neural activity [26-28].

When combined with BOLD measures, ASL measures of CBF can be used to derive estimates of functional changes in the cerebral metabolic rate of oxygen ($CMRO_2$), which has been shown in animal studies to be correlated with functional changes in neuronal spiking frequency [29]. In human fMRI studies, the use of simultaneous measurements of CBF and BOLD responses to a hypercapnic stimulus (administered carbon dioxide) can provide information that is then used to calibrate the BOLD response and estimate functional changes in $CMRO_2$ [30]. This approach has been used to demonstrate a linear coupling in the visual cortex between functional changes in CBF and $CMRO_2$ [31].

Simultaneous measures of CBF and BOLD with ASL are also useful for understanding the mechanisms underlying the BOLD response. For example, the BOLD responses in the supplementary motor area shown in Figure 5 exhibit pronounced transients at stimulus onset and cessation that are not observed in the CBF data, suggesting that the BOLD transients may primarily reflect vascular as opposed to neural effects. Similarly, ASL measurements have been used to examine whether post-stimulus undershoots in the BOLD signal are due primarily to a slow return to baseline in cerebral blood volume or a prolonged elevation of CMRO₂ [32, 33].

Insensitivity to Low-Frequency Noise

Low frequency drifts are present in most fMRI time series data and tend to reduce the statistical power of BOLD experiments. As discussed in a previous section, perfusion time series are formed from the filtered subtraction of control and tag images. This subtraction process greatly attenuates the low frequency drifts and can make ASL more sensitive than BOLD for experimental paradigms with long periods. For example, one study has shown that the sensitivity of ASL is greater than that of BOLD when the alternating period between task and control is greater than a few minutes [28]. In a recent study assessing the effects of psychological stress on CBF, the insensitivity of ASL to low frequency drifts enabled the investigators to demonstrate a decrease in CBF that persisted for at least 8 minutes after the completion of a stressful task [34].

Spatial Localization

Because CBF directly measures the amount of arterial blood that has been delivered to the capillary beds, it has been hypothesized that the functional CBF signal may be more localized to the sites of neuronal activation than the BOLD signal. With the quantitative ASL methods described above, the measured CBF signal is primarily from small arterioles, capillaries, and brain tissue. There is relatively little signal in the arteries because the inversion delays are chosen to allow enough time for the blood to flow to the target tissue. In addition, there is relatively little outflow of the tagged blood into the venous circulation, because (a) the inversion delays are on the order of the T_1 of blood, which is much less than the capillary transit time, and (b) there is rapid exchange of water between the vascular and tissue compartments. By contrast, the BOLD signal derives primarily from veins and their surrounding tissues. Evidence in support of improved localization with ASL comes from a study which found that the average T_1 of voxels that demonstrate a large ASL signal was close to that of gray matter, while the average T_1 of voxels demonstrating intermediate between those of gray matter, blood, and CSF [35]. Similarly, in a study of visual orientation columns in the cat brain, it was found that the ASL signal provided a more convincing functional map of these very high resolution structures than the BOLD signal [36].

Summary

Perfusion fMRI using arterial spin labeling offers a useful complement to the standard BOLD techniques. ASL methods provide a quantitative measure of CBF that has the potential to better characterize the magnitude and localize the sites of the underlying neuronal activity. In addition, the quantitative CBF measures can be used to compensate for differences in BOLD that might be due to differences in baseline CBF. The two most important limitations of ASL techniques for fMRI are that both the temporal resolution and the sensitivity of ASL are lower than those of the BOLD contrast mechanism.

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